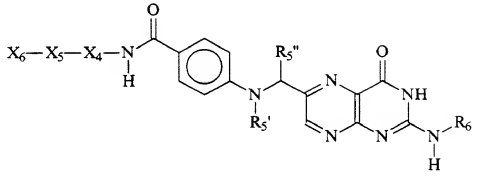
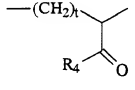
What is claimed is:

1. A compound of the formula:



wherein:

X_4 is $-CH(X_{4'})$ or a group of formula:



$X_{4'}$ is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

X_5 is $-N(X_{6'})C(O)-$, $-C(O)NH-$, $-NHC(O)-$, $-OC(O)NH-$, $-C(S)NH-$, $-SC(S)NH-$, $-SC(O)NH-$, $-OC(S)NH-$, $-C(O)O-$, $-C(O)(CH_2)_n-$ or a bond;

n is an integer from 1 to 50;

each X_6 and $X_{6'}$ is, independently, hydrogen or a hydrocarbyl group selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_6-C_{14} aralkyl, C_3-C_{14} cycloalkyl, C_5-C_{14} fused cycloalkyl, C_4-C_{14} heterocycle, C_4-C_{14} heterocyclylalkyl, C_4-C_{14} heteroaryl and C_4-C_{14} heteroarylalkyl; wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT,

alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that X_6 is not hydrogen;

R_4 is a hydroxyl group or a protected hydroxyl group;

R_5, is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl or an amino-protecting group

R_5,, is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_6-C_{14} aralkyl, C_3-C_{14} cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

R_6 is hydrogen or an amino protecting group; and

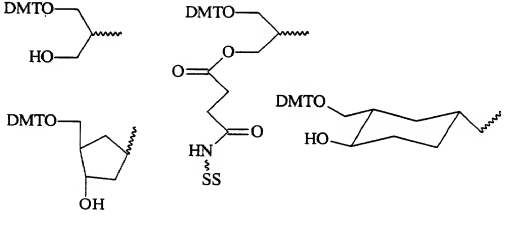
t is 1 or 2.

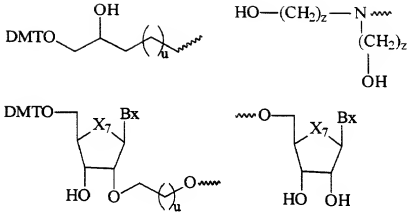
2. The compound of claim 1 wherein said amino acid is amino caproic acid.

3. The compound of claim 1 connected to an oligonucleotide by a disulfide group.

4. The compound of claim 1 wherein said X_4, is the side chain of glutamic acid.

5. The compound of claim 1 wherein said X_6 has one of the formulas:





wherein:

SS is a solid support;

X_7 is O or CH_2;

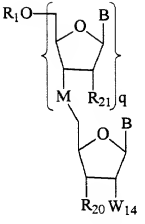
Bx is a nucleobase, C_4-C_{14} heterocyclyl or hydrogen;

z is an integer from 1 to 50; and

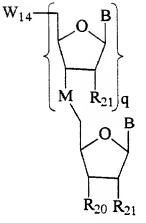
u is an integer from 2 to 5.

6. The compound of claim 1 wherein said X_6 is attached to a solid support.

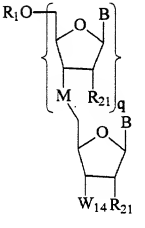
7. A compound having formula XVIA, XVIB, XVIC or XVID:

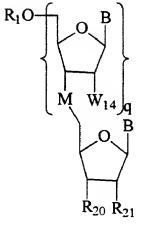


XVIA



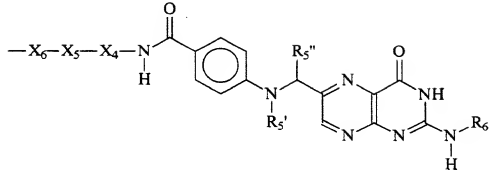
XVIC





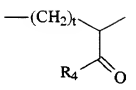
wherein:

W_{14} has the formula:



wherein:

X_4 is $-CH(X_{4'})$ or a group of formula:



X_4, is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

t is 1 or 2;

X_5 is $-N(X_6,)C(O)-$, $-C(O)NH-$, $-NHC(O)-$, $-OC(O)NH-$, $-C(S)NH-$, $-SC(S)NH-$, $-SC(O)NH-$, $-OC(S)NH-$, $-C(O)O-$, $-C(O)(CH_2)_n-$ or a bond;

n is an integer from 1 to 50;

each X_6 and X_6, is, independently, a bond, hydrogen or a hydrocarbyl group selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_6-C_{14} aralkyl, C_3-C_{14} cycloalkyl, C_5-C_{14} fused cycloalkyl, C_4-C_{14} heterocycle, C_4-C_{14} heterocyclylalkyl, C_4-C_{14} heteroaryl and C_4-C_{14} heteroarylalkyl; wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that X_6 is not hydrogen and X_6, is not a bond;

R_1 is hydrogen or a hydroxyl protecting group;

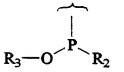
R_4 is a hydroxyl group or a protected hydroxyl group;

each R_5, and R_{40} is, independently, hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl or an amino-protecting group

R_5,, is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_6-C_{14} aralkyl, C_3-C_{14} cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

R_6 is hydrogen or an amino protecting group;

R_{20} is hydrogen or a group of formula:



R_2 is $-N(R_7)_2$, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

R_7 is straight or branched chain alkyl having from 1 to 10 carbons;

R_3 is a phosphorus protecting group;

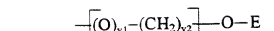
R_{21} is hydrogen, hydroxyl, fluoro or a group of formula $Z-R_{22}-(R_{23})_v$;

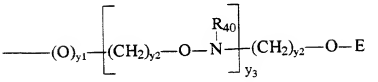
Z is O, S, NH or $N-R_{22}-(R_{23})_v$;

R_{22} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

or R_{21} has one of the formulas:





wherein:

y1 is 0 or 1;

each y2 is, independently, 0 to 10;

y3 is 1 to 10;

E is $N(R_{41})(R_{42})$ or $N=C(R_{41})(R_{42})$;

each R_{41} and each R_{42} is independently H, C_1-C_{10} alkyl, a nitogen protecting group, or R_{41} and R_{42} taken together form a nitrogen protecting group; or R_{41} and R_{42} taken together with the N or C atom to which they are attached form a ring structure that can include at least one heterotom selected from N and O;

B is a nucleobase;

M is an optionally protected internucleoside linkage;

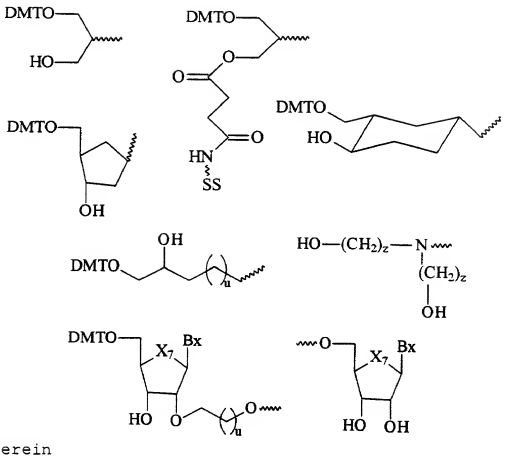
q is from zero to about 50; and

v is from zero to about 10.

8. The compound of claim 7 wherein said amino acid is amino caproic acid.

9. The compound of claim 7 wherein said X_4 is the side chain of glutamic acid.

10. The compound of claim 7 wherein said X_6 has one of the formulas:



wherein

SS is a solid support;

X_7 is O or CH_2;

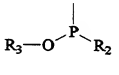
Bx is a nucleobase, C_4-C_{14} heterocyclyl or hydrogen;

z is an integer from 1 to 50; and

u is an integer from 2 to 5.

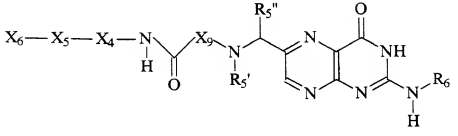
11. The compound of claim 7 wherein said R_1 is dimethoxytrityl.

12. The compound of claim 7 wherein said R_{20} is a group of formula:



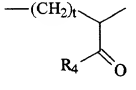
wherein R_2 is diisopropylamino and R_3 is β-cyanoethyl.

13. A compound of the formula:



wherein:

X_4 is $-CH(X_{4'})$ or a group of formula:



$X_{4'}$ is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

X_5 is $-N(X_{6'})C(O)-$, $-C(O)NH-$, $-NHC(O)-$, $-OC(O)NH-$, $-C(S)NH-$, $-SC(S)NH-$, $-SC(O)NH-$, $-OC(S)NH-$, $-C(O)O-$, $-C(O)(CH_2)_n-$ or a bond;

n is an integer from 1 to 50;

each X_6, $X_{6'}$ and X_9 is, independently, a bond, hydrogen or a hydrocarbyl group selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_6-C_{14} aralkyl, C_3-C_{14} cycloalkyl, C_5-C_{14} fused cycloalkyl, C_4-C_{14} heterocycle, C_4-C_{14} heterocyclylalkyl, C_4-C_{14} heteroaryl and C_4-C_{14} heteroarylalkyl; wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate,

sulfonamide, thiol, and thioalkoxy; provided that each of X_6 and $X_{6'}$ is not a bond and X_6 is not hydrogen;

R_4 is a hydroxyl group or a protected hydroxyl group;

R_5' is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl or an amino-protecting group

$R_{5''}$ is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_6-C_{14} aralkyl, C_3-C_{14} cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

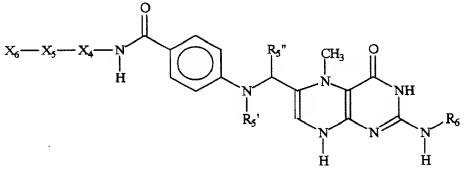
R_6 is hydrogen or an amino protecting group; and

t is 1 or 2.

14. The compound of claim 13 wherein said amino acid is aminocaproic acid

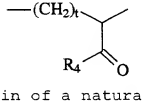
15. The compound of claim 13 connected to an oligonucleotide by a disulfide group.

16. A compound of the formula:



wherein:

X_4 is -CH($X_{4'}$) or a group of formula:



$X_{4'}$ is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

X_5 is $-N(X_{6'})C(O)-$, $-C(O)NH-$, $-NHC(O)-$, $-OC(O)NH-$, $-C(S)NH-$, $-SC(S)NH-$, $-SC(O)NH-$, $-OC(S)NH-$, $-C(O)O-$, $-C(O)(CH_2)_n-$ or a bond;

n is an integer from 1 to 50;

each X_6 and $X_{6'}$ is, independently, hydrogen or a hydrocarbyl group selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_8-C_{14} aralkyl, C_3-C_{14} cycloalkyl, C_5-C_{14} fused cycloalkyl, C_4-C_{14} heterocycle, C_4-C_{14} heterocyclylalkyl, C_4-C_{14} heteroaryl and C_4-C_{14} heteroarylalkyl; wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and optionally substituted with oxo, acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that X_6 is not hydrogen;

R_4 is a hydroxyl group or a protected hydroxyl group;

$R_{5'}$ is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl or an amino-protecting group

$R_{5''}$ is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_6-C_{14} aralkyl, C_3-C_{14} cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

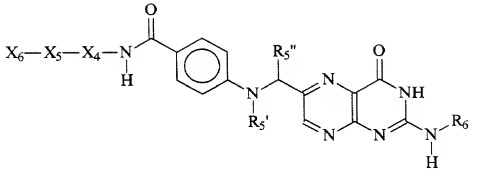
R_6 is hydrogen or an amino protecting group; and

t is 1 or 2.

17. The compound of claim 16 wherein said amino acid is aminocaproic acid.

18. The compound of claim 16 connected to an oligonucleotide by a disulfide group.

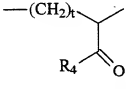
19. A method of preparing compounds of formula XVII:



XVII

wherein:

X_4 is $-CH(X_{4'})$ or a group of formula:



$X_{4'}$ is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

X_5 is $-N(X_{6'})C(O)-$, $-C(O)NH-$, $-NHC(O)-$, $-OC(O)NH-$, $-C(S)NH-$, $-SC(S)NH-$, $-SC(O)NH-$, $-OC(S)NH-$, $-C(O)O-$, $-C(O)(CH_2)_n-$ or a bond;

n is an integer from 1 to 50;

each X_6 and $X_{6'}$ is, independently, hydrogen or a hydrocarbyl group selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_6-C_{14} aralkyl, C_3-C_{14} cycloalkyl, C_5-C_{14} fused cycloalkyl, C_4-C_{14} heterocycle, C_4-C_{14} heterocyclylalkyl, C_4-C_{14} heteroaryl and C_4-C_{14} heteroarylalkyl; wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate,

sulfonamide, thiol, and thioalkoxy; provided that X_6 is not hydrogen;

R_4 is a hydroxyl group or a protected hydroxyl group;

$R_{5'}$ is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl or an amino-protecting group

$R_{5''}$ is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_6-C_{14} aralkyl, C_3-C_{14} cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

R_6 is hydrogen or an amino protecting group; and

t is 1 or 2;

comprising the steps of:

(a) providing a hydroxy compound of formula:

$$X_6\text{-}X_5\text{-}H$$

(b) protecting said hydroxyl groups of X_6 with protecting groups to form a protected hydroxy compound;

(c) reacting said protected hydroxy compound with an amino-protected amino acid to form a covalently linked hydroxy compound of formula:

$$X_6\text{-}X_5\text{-}X_4\text{-}NH\text{-}Ag$$

wherein Ag is an amino protecting group;

(d) cleaving the amino-protecting group of said covalently linked hydroxy compound to form a hydroxy compound bearing a deprotected amino group and having formula:

$$X_6\text{-}X_5\text{-}X_4\text{-}NH_2$$

(e) reacting said amino group with a folate moiety; and

(f) cleaving the protecting groups on said hydroxyl groups of step (b) to form a compound of formula XVII.

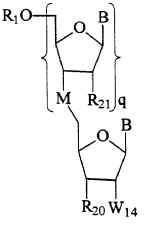
20. The method of claim 19 further comprising the steps of:

(g) protecting one of said hydroxyl groups of X_6 with a dimethoxytrityl group; and

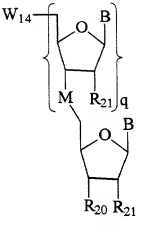
(h) phosphitylating the other of said hydroxyl groups of

X_6.

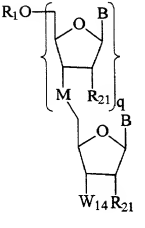
21. A compound having formula XVIA, XVIB, XVIC or XVID:



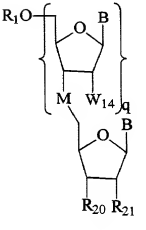
XVIA



XVIC



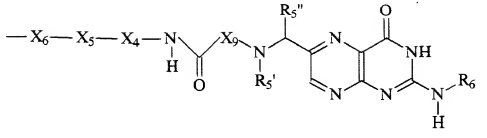
XVIB



XVID

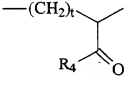
wherein:

W_{14} has the formula:



wherein:

X_4 is $-CH(X_{4'})$ or a group of formula:



$X_{4'}$ is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

t is 1 or 2;

X_5 is $-N(X_{6'})C(O)-$, $-C(O)NH-$, $-NHC(O)-$, $-OC(O)NH-$, $-C(S)NH-$, $-SC(S)NH-$, $-SC(O)NH-$, $-OC(S)NH-$, $-C(O)O-$, $-C(O)(CH_2)_n-$ or a bond;

n is an integer from 1 to 50;

each X_6, $X_{6'}$ and X_9 is, independently, a bond, hydrogen or a hydrocarbyl group selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_8-C_{14} aralkyl, C_3-C_{14} cycloalkyl, C_5-C_{14} fused cycloalkyl, C_4-C_{14} heterocycle, C_4-C_{14} heterocyclylalkyl, C_4-C_{14} heteroaryl and C_4-C_{14} heteroarylalkyl; wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate,

sulfonamide, thiol, and thioalkoxy; provided that each X_6 and X_9 is not hydrogen and $X_{6'}$ is not a bond;

R_1 is hydrogen or a hydroxyl protecting group;

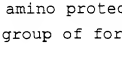
R_4 is a hydroxyl group or a protected hydroxyl group;

each $R_{5'}$ and R_{40} is, independently, hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl or an amino-protecting group

$R_{5''}$ is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_6-C_{14} aralkyl, C_3-C_{14} cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

R_6 is hydrogen or an amino protecting group;

R_{20} is hydrogen or a group of formula:



R_2 is $-N(R_7)_2$, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

R_7 is straight or branched chain alkyl having from 1 to 10 carbons;

R_3 is a phosphorus protecting group;

R_{21} is hydrogen, hydroxyl, fluoro or a group of formula $Z\text{-}R_{22}\text{-}(R_{23})_v$;

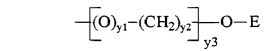
Z is O, S, NH or $N\text{-}R_{22}\text{-}(R_{23})_v$;

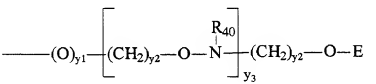
R_{22} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide,

polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

or R_{21} has one of the formulas:





wherein:

y1 is 0 or 1;

each y2 is, independently, 0 to 10;

y3 is 1 to 10;

E is $N(R_{41})(R_{42})$ or $N{=}C(R_{41})(R_{42})$;

each R_{41} and each R_{42} is independently H, C_1-C_{10} alkyl, a nitogen protecting group, or R_{41} and R_{42} taken together form a nitrogen protecting group; or R_{41} and R_{42} taken together with the N or C atom to which they are attached form a ring structure that can include at least one heterotom selected from N and O;

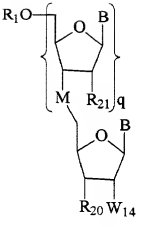
B is a nucleobase;

M is an optionally protected internucleoside linkage;

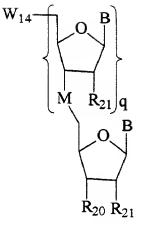
q is from zero to about 50; and

v is from zero to about 10.

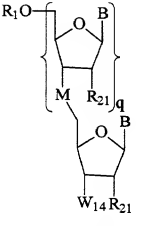
22. A compound having formula XVIA, XVIB, XVIC or XVID:



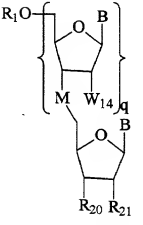
XVIA



XVIC



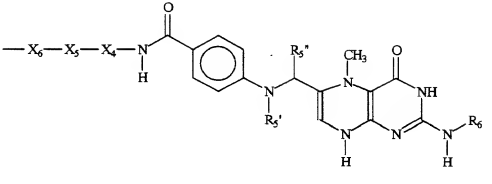
XVIB



XVID

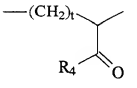
wherein:

W_{14} has the formula:



wherein:

X_4 is $-CH(X_{4'})$ or a group of formula:



$X_{4'}$ is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

t is 1 or 2;

X_5 is $-N(X_{6'})C(O)-$, $-C(O)NH-$, $-NHC(O)-$, $-OC(O)NH-$, $-C(S)NH-$, $-SC(S)NH-$, $-SC(O)NH-$, $-OC(S)NH-$, $-C(O)O-$, $-C(O)(CH_2)_n-$ or a bond;

n is an integer from 1 to 50;

each X_6 and $X_{6'}$ is, independently, a bond, hydrogen or a hydrocarbyl group selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_6-C_{14} aralkyl, C_3-C_{14} cycloalkyl, C_5-C_{14} fused cycloalkyl, C_4-C_{14} heterocycle, C_4-C_{14} heterocyclylalkyl, C_4-C_{14} heteroaryl and C_4-C_{14} heteroarylalkyl; wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that X_6 is not hydrogen and $X_{6'}$ is not a bond;

R_1 is hydrogen or a hydroxyl protecting group;

R_4 is a hydroxyl group or a protected hydroxyl group;

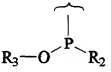
each $R_{5'}$ and R_{40} is, independently, hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl or an amino-protecting group

$R_{5''}$ is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_6-C_{14} aralkyl, C_3-C_{14} cycloalkyl, formyl,

aminoalkyl or hydroxymethyl;

R_6 is hydrogen or an amino protecting group;

R_{20} is hydrogen or a group of formula:



R_2 is $-N(R_7)_2$, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

R_7 is straight or branched chain alkyl having from 1 to 10 carbons;

R_3 is a phosphorus protecting group;

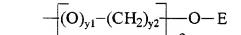
R_{21} is hydrogen, hydroxyl, fluoro or a group of formula $Z-R_{22}-(R_{23})_v$;

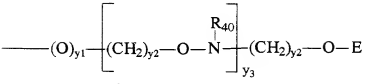
Z is O, S, NH or $N-R_{22}-(R_{23})_v$;

R_{22} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

or R_{21} has one of the formulas:





wherein:

y1 is 0 or 1;

each y2 is, independently, 0 to 10;

y3 is 1 to 10;

E is $N(R_{41})(R_{42})$ or $N=C(R_{41})(R_{42})$;

each R_{41} and each R_{42} is independently H, C_1-C_{10} alkyl, a nitogen protecting group, or R_{41} and R_{42} taken together form a nitrogen protecting group; or R_{41} and R_{42} taken together with the N or C atom to which they are attached form a ring structure that can include at least one heterotom selected from N and O;

B is a nucleobase;

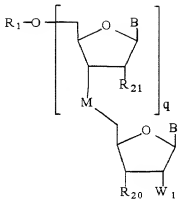
M is an optionally protected internucleoside linkage;

q is from zero to about 50; and

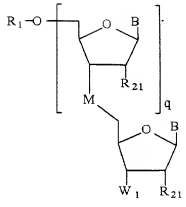
v is from zero to about 10.

23. A synthetic method comprising the steps of:

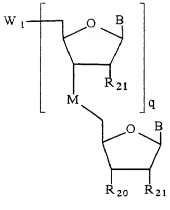
(a) providing a compound of formula IA, IB, IC or ID:



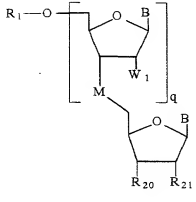
IA



IB



IC



ID

wherein:

W_1 is a linking group, O, NH, or S;

R_1 is H or a hydroxyl protecting group;

B is a nucleobase;

each R_{21} is H, OH, F, or a group of formula $Z\text{-}R_{22}\text{-}(R_{23})_v$;

Z is O, S, NH, or $N\text{-}R_{22}\text{-}(R_{23})_v$

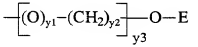
R_{22} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

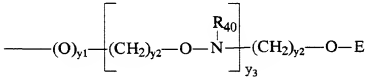
R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide,

polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

v is from 0 to about 10;

or R_{21} has one of the formulas:





wherein:

y1 is 0 or 1;

y2 is 0 to 10;

y3 is 1 to 10;

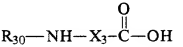
E is $N(R_{41})(R_{42})$ or $N=C(R_{41})(R_{42})$;

each R_{41} and each R_{42} is independently H, C_1-C_{10} alkyl, a nitogen protecting group, or R_{41} and R_{42} taken together form a nitrogen protecting group; or R_{41} and R_{42} taken together with the N or C atom to which they are attached form a ring structure that can include at least one heterotom selected from N and O;

q is from 0 to about 50;

M is an optionally protected internucleoside linkage;

(b) reacting said compound of formula I with a compound of formula II:

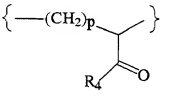


II

wherein:

R_{30} is an amino protecting group;

X_3 is $-CH(Z_1)-$ or a group of Formula XI:

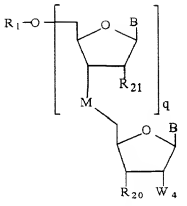


XI

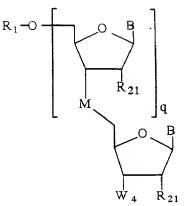
Z_1 is the sidechain of a naturally occurring amino acid, or a protected sidechain of a naturally occurring amino acid;

p is 1 or 2;

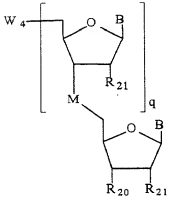
to form a compound of formula IVA, IVB, IVC, or IVD:



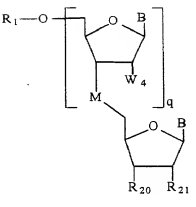
IV A



IV B



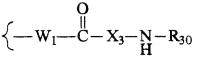
IV C



IV D

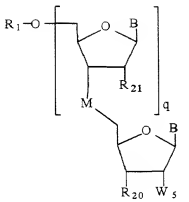
wherein:

W_4 has the formula:

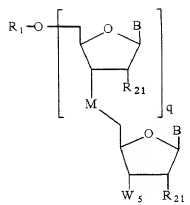


and

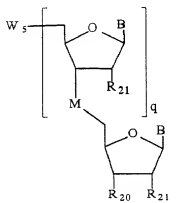
treating said compound of formula IVA, IVB, IVC or IVD with a deprotecting reagent to form a compound of formula VA, VB, VC or VD:



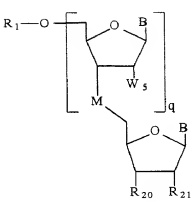
VA



VB

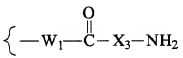


VC

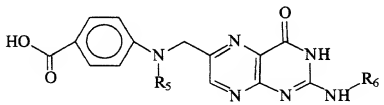


VD

wherein W_5 has the formula:



24. The method of claim 23 further comprising condensing said compound of formula V with a compound of formula VI:

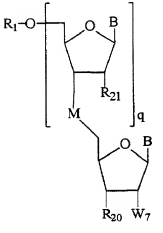


VI

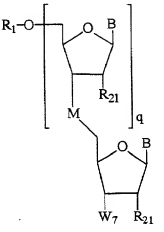
wherein:

R_5 is H or an amino protecting group;
R_6 is H or an amino protecting group;

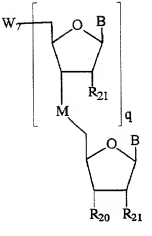
to form a compound of formula VIIA, VIIB, VIIC, or VIID:



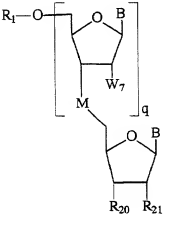
VIIA



VIIB

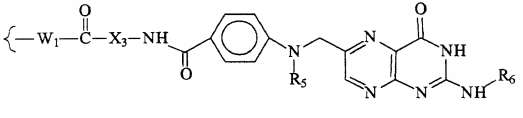


VIIC

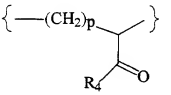


VIID

wherein W_7 has the formula:



25. The method of claim 24 wherein X_3 is a group of formula XI:



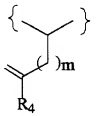
XI

wherein:

p is 1 or 2;

R_4 is a hydroxyl group, or a protected hydroxy group;

or X_3 is a group of formula XII:



XII

wherein m is 1 or 2.

26. The method of claim 25 wherein q is 0.

27. The method of claim 25 wherein R_{30} is fluorene-9-yl methoxycarbonyl.

28. The method of claim 25 wherein X_3 is a group of formula XI.

29. The method of claim 25 wherein W_1 has the formula $-O-(CH_2)_n-NH-$, wherein n is from 1 to about 10.

30. The method of claim 29 wherein n is 6.

31. The method of claim 25 wherein X_3 is a group of formula XII.

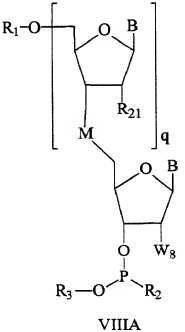
32. The method of claim 31 wherein W_1 has the formula $-O-(CH_2)_n-NH-$, wherein n is from 1 to about 10.

33. The method of claim 32 wherein n is 6.

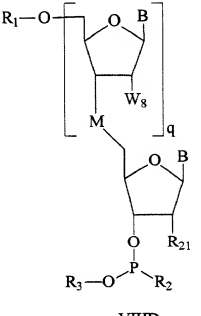
34. The method of claim 28 wherein R_1 is dimethoxytrityl, W_1 has the formula $-O-(CH_2)_n-NH-$ where n is 6, p is 2, R_4 is t-butoxy, R_5 is trifluoroacetoyl, R_6 is $-C(=O)-CH(CH_3)_2$, and R_{30} is FMOC.

35. The method of claim 31 wherein R_1 is dimethoxytrityl, A has the formula $-O-(CH_2)_n-NH-$ where n is 6, m is 2, R_4 is t-butoxy, R_5 is trifluoroacetoyl, R_6 is $-C(=O)-CH(CH_3)_2$, and R_{30} is FMOC.

36. The method of claim 24 further comprising contacting said compound of formula VIIA or VIID with a phosphitylating reagent to form a compound of formula VIIIA or VIIIAD:

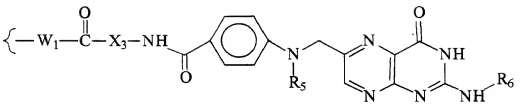


VIIIA



VIIID

wherein W_7 has the formula:



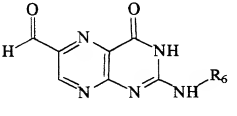
37. The method of claim 36 wherein X_3 has the formula XI.

38. The method of claim 36 wherein X_3 has the formula XII.

39. The method of claim 37 wherein R_1 is dimethoxytrityl, W_1 has the formula $-O-(CH_2)_n-NH-$ where n is 6, p is 2, R_4 is t-butoxy, R_5 is trifluoroacetoyl, R_6 is $-C(=O)-CH(CH_3)_2$, and R_{30} is FMOC.

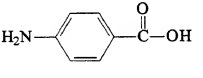
40. The method of claim 38 wherein R_1 is dimethoxytrityl, W_1 has the formula $-O-(CH_2)_n-NH-$ where n is 6, m is 2, R_4 is t-butoxy, R_5 is trifluoroacetoyl, R_6 is $-C(=O)-CH(CH_3)_2$, and R_{30} is FMOC.

41. The method of claim 25 wherein said compound of formula VI is prepared by the steps of reacting a compound of formula IX:



IX

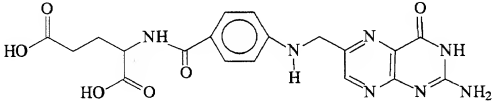
with a compound of formula X:



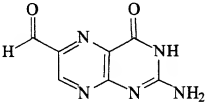
X

and treating the product of said reaction with a protecting group reagent to form said compound of formula VI.

42. The method of claim 26 wherein said compound IX is prepared by reacting folic acid:



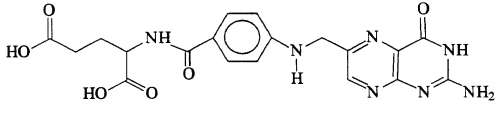
with a reagent effective to form pterin aldehyde:



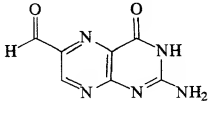
and

protecting the amino group of said pterin aldehyde.

43. A method for the preparation of a folic acid derivative comprising the steps of reacting folic acid:

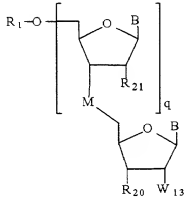


with a reagent effective to form pterin aldehyde:

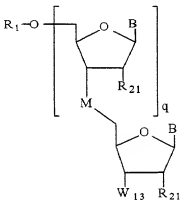


44. The method of claim 43 further comprising protecting the amino group of said pterin aldehyde.

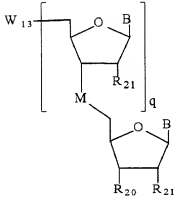
45. A compound having the formula XIIIA, XIIB, XIIIC or XIIID:



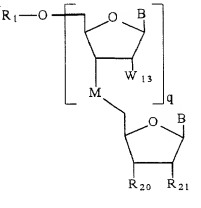
XIIIA



XIIIB



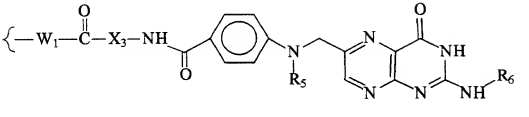
XIIIC



XIIID

wherein:

W_{13} has the formula:



R_1 is H or a hydroxyl protecting group;

B is a nucleobase;

each R_{21} is H, OH, F, or a group of formula $Z\text{-}R_{22}\text{-}(R_{23})_v$;

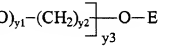
Z is O, S, NH or $N\text{-}R_{22}\text{-}(R_{23})_v$;

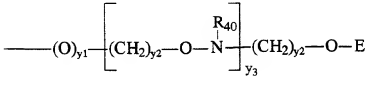
R_{22} is $C_1\text{-}C_{20}$ alkyl, $C_2\text{-}C_{20}$ alkenyl, or $C_2\text{-}C_{20}$ alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol,

keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

or R_{21} has one of the formulas:





wherein:

y1 is 0 or 1;

y2 is 0 to 10;

y3 is 1 to 10;

E is $N(R_{41})(R_{42})$ or $N=C(R_{41})(R_{42})$;

each R_{41} and each R_{42} is independently H, C_1-C_{10} alkyl, a nitogen protecting group, or R_{41} and R_{42} taken together form a nitrogen protecting group; or R_{41} and R_{42} taken together with the N or C atom to which they are attached form a ring structure that can include at least one heterotom selected from N and O;

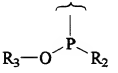
v is from 0 to about 10;

q is from 0 to about 50;

M is an optionally protected internucleoside linkage;

W_1 is a linking group, O, NH or S;

R_{20} is H or a group of Formula:



R_2 is $-N(R_7)_2$, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

R_7 is straight or branched chain alkyl having from 1 to 10 carbons;

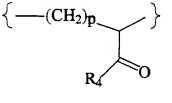
R_3 is a phosphorus protecting group;

n is from 1 to about 10;

R_5 is H or an amino protecting group;

R_6 is H or an amino protecting group;

X_3 is $-CH(Z_1)-$ or a group of Formula XI:



XI

Z_1 is the sidechain of a naturally occurring amino acid, or a protected sidechain of a naturally occurring amino acid;

p is 1 or 2; and

R_4 is a hydroxyl group, or a protected hydroxy group.

46. The compound of claim 45 wherein W_1 is $-O-(CH_2)_n-NH-$ where n is from 1 to about 10.

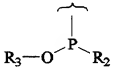
47. The compound of claim 45 wherein n is 6.

48. The compound of claim 45 wherein R_1 is

dimethoxytrityl, R_5 is trifluoroacetoyl, and R_6 is $-C(=O)-CH(CH_3)_2$, and R_4 is t-butoxy.

49. The compound of claim 45 wherein q is 0.

50. The compound of claim 45 wherein R_{20} is a group of formula:



wherein R_3 is β-cyanoethyl, and R_2 is diisopropylamino.

51. The compound of claim 50 wherein W_1 is $-O-(CH_2)_6-NH-$, R_1 is dimethoxytrityl, R_5 is trifluoroacetoyl, R_6 is $-C(=O)-CH(CH_3)_2$, and R_4 is t-butoxy.

52. The compound of claim 50 wherein q is 0.

53. The compound of claim 45 wherein X_3 has the formula XI.

54. The compound of claim 53 wherein p is 2.

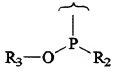
55. The compound of claim 54 wherein W_1 is $-O-(CH_2)_6-NH-$.

56. The compound of claim 55 wherein R_4 is t-butoxy.

57. The compound of claim 56 wherein R_1 is dimethoxytrityl, R_5 is trifluoroacetoyl, and R_6 is $-C(=O)-CH(CH_3)_2$.

58. The compound of claim 57 wherein q is 0.

59. The compound of claim 58 wherein R_{20} is a group of formula:

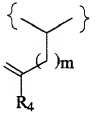


wherein R_3 is β-cyanoethyl, and R_2 is diisopropylamino.

60. The compound of claim 57 wherein R_{20} is H.

61. The compound of claim 60 wherein q is 0.

62. The compound of claim 45 wherein X_3 has the formula XII:



XII

wherein m is 1 or 2.

63. The compound of claim 62 wherein m is 2.

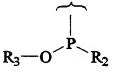
64. The compound of claim 63 wherein W_1 is $-O-(CH_2)_6-NH-$.

65. The compound of claim 54 wherein R_4 is t-butoxy.

66. The compound of claim 65 wherein R_1 is dimethoxytrityl, R_5 is trifluoroacetoyl, and R_6 is $-C(=O)-CH(CH_3)_2$.

67. The compound of claim 66 wherein q is 0.

68. The compound of claim 67 wherein R_{20} is a group of formula:

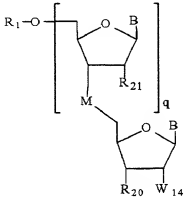


where R_3 is β-cyanoethyl, and R_2 is diisopropylamino.

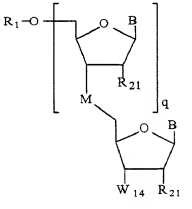
69. The compound of claim 45 wherein R_{20} is H.

70. The compound of claim 69 wherein q is 0.

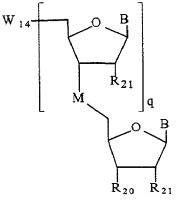
71. A composition comprising a compound of claim 54, said composition being substantially free of a compound of formula XIVA, XIVB, XIVC, or XIVD:



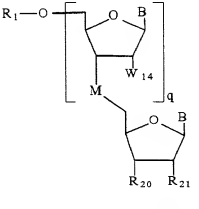
XIVA



XIVB



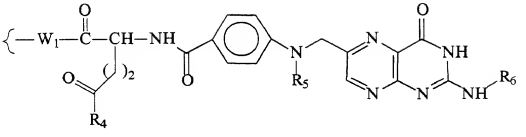
XIVC



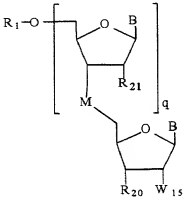
XIVD

wherein:

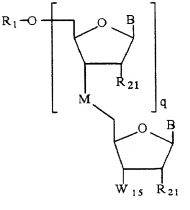
W_{14} has the formula:



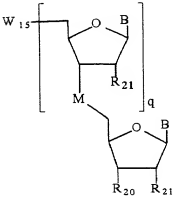
72. A composition comprising a compound of claim 63, said composition being substantially free of a compound of formula XVA, XVB, XVC or XVD:



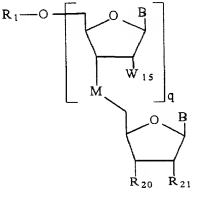
XVA



XVB

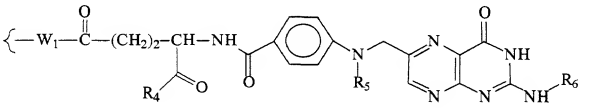


XVC

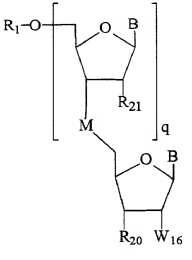


XVD

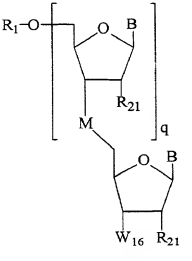
wherein W_{15} has the formula:



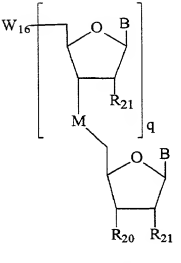
73. A compound having the formula XVIA, XVIB, XVIC or XVID:



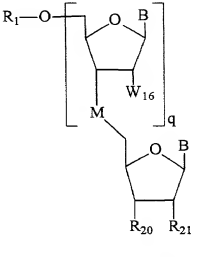
XVIA



XVIB



XVIC



XVID

wherein:

W_{16} has the formula:

R_1 is H or a hydroxyl protecting group;

B is a nucleobase;

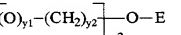
each R_{21} is H, OH, F, or a group of formula $Z\text{-}R_{22}\text{-}(R_{23})_v$;

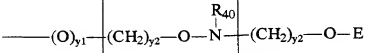
Z is O, S, NH or $N\text{-}R_{22}\text{-}(R_{23})_v$;

R_{22} is $C_1\text{-}C_{20}$ alkyl, $C_2\text{-}C_{20}$ alkenyl, $C_2\text{-}C_{20}$ alkynyl, $C_1\text{-}C_{20}$ akoxy, $C_2\text{-}C_{20}$ alkenyloxy, or $C_2\text{-}C_{20}$ alkynyloxy;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

or R_{21} has one of the formulas:





wherein:

y1 is 0 or 1;

y2 is 0 to 10;

y3 is 1 to 10;

E is $N(R_{41})(R_{42})$ or $N=C(R_{41})(R_{42})$;

each R_{41} and each R_{42} is independently H, C_1-C_{10} alkyl, a nitogen protecting group, or R_{41} and R_{42} taken together form a nitrogen protecting group; or R_{41} and R_{42} taken together with the N or C atom to which they are attached form a ring structure that can include at least one heterotom selected from N and O;

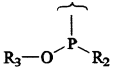
v is from 0 to about 10;

q is from 0 to about 50;

M is an optionally protected internucleoside linkage;

W_1 is a linking group;

R_{20} is H or a group of Formula:



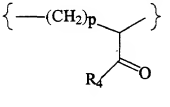
R_2 is $-N(R_7)_2$, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

R_7 is straight or branched chain alkyl having from 1 to 10 carbons;

R_3 is a phosphorus protecting group;

n is from 1 to about 10;

X_3 is $-CH(Z_1)-$ or a group of Formula XI:



XI

Z_1 is the sidechain of a naturally occurring amino acid, or a protected sidechain of a naturally occurring amino acid; and

p is 1 or 2.

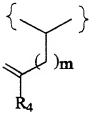
74. The compound of claim 73 wherein X_3 has the formula XI.

75. The compound of claim 74 wherein p is 2.

76. The compound of claim 75 wherein W_1 is $-O-(CH_2)_n-NH-$ wherein n is from 1 to about 10.

77. The compound of claim 76 wherein n is 6.

78. The compound of claim 73 wherein X_3 has the formula XII:



XII

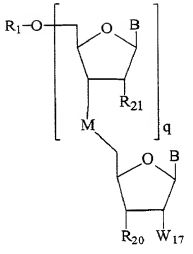
wherein m is 1 or 2.

79. The compound of claim 78 wherein m is 2.

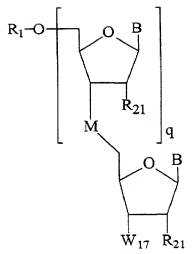
80. The compound of claim 79 wherein W_1 is $-O-(CH_2)_n-NH-$ wherein n is from 1 to about 10.

81. The compound of claim 80 wherein n is 6.

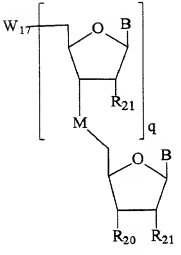
82. A compound having the formula XVIIA, XVIIB, XVIIC or XVIID:



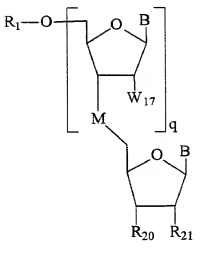
XVIIA



XVIIB



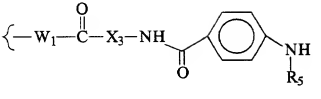
XVIIC



XVIID

wherein:

W_{17} has the formula:



R_1 is H or a hydroxyl protecting group;

B is a nucleobase;

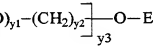
each R_{21} is H, OH, F, or a group of formula $Z\text{-}R_{22}\text{-}(R_{23})_v$;

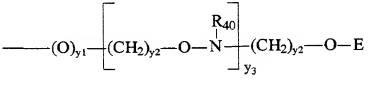
Z is O, S, NH or N-R_{22}-$(R_{23})_v$;

R_{22} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

or R_{21} has one of the formulas:





wherein:

y1 is 0 or 1;

y2 is 0 to 10;

y3 is 1 to 10;

E is $N(R_{41})(R_{42})$ or $N{=}C(R_{41})(R_{42})$;

each R_{41} and each R_{42} is independently H, C_1-C_{10} alkyl, a nitogen protecting group, or R_{41} and R_{42} taken together form a nitrogen protecting group; or R_{41} and R_{42} taken together with the N or C atom to which they are attached form a ring structure that can include at least one heterotom selected from N and O;

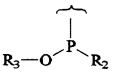
v is from 0 to about 10;

q is from 0 to about 50;

M is an optionally protected internucleoside linkage;

W_1 is a linking group, O, NH or S;

R_{20} is H or a group of formula:



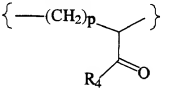
R_2 is $-N(R_7)_2$, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

R_7 is straight or branched chain alkyl having from 1 to 10 carbons;

R_3 is a phosphorus protecting group;

n is from 1 to about 10;

X_3 is $-CH(Z_1)-$ or a group of formula XI:



XI

Z_1 is the sidechain of a naturally occurring amino acid, or a protected sidechain of a naturally occurring amino acid;

p is 1 or 2; and

R_5 is H or an amino protecting group.

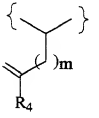
83. The compound of claim 82 wherein X_3 has the formula XI.

84. The compound of claim 83 wherein p is 2.

85. The compound of claim 84 wherein W_1 is $-O-(CH_2)_n-NH-$ wherein n is from 1 to about 10.

86. The compound of claim 85 wherein n is 6.

87. The compound of claim 82 wherein X_3 has the formula XII:



XII

wherein m is 1 or 2.

88. The compound of claim 87 wherein m is 2.

89. The compound of claim 88 wherein W_1 is $-O-(CH_2)_n-NH-$ wherein n is from 1 to about 10.

90. The compound of claim 89 wherein n is 6.

91. A folate conjugate comprising a folate moiety covalently linked to an amino acid, said amino acid further connected to a hydrocarbyl group, said hydrocarbyl group bearing at least two hydroxyl groups.

92. An oligonucleotide-folate conjugate comprising a folate moiety covalently linked to an amino acid, said amino acid being connected to a hydrocarbyl group, said hydrocarbyl group further connected to an oligonucleotide, said hydrocarbyl group bearing at least two hydroxyl groups.

93. The compound of claim 7 wherein said R_4 is a hydroxyl group protected with C_1-C_{10} alkyl, C_2-C_{10} alkenyl or C_2-C_{20} alkynyl.

94. The compound of claim 13 wherein said R_4 is a

hydroxyl group protected with C_1-C_{10} alkyl, C_2-C_{10} alkenyl or C_2-C_{20} alkynyl.

95. The compound of claim 16 wherein said R_4 is a hydroxyl group protected with C_1-C_{10} alkyl, C_2-C_{10} alkenyl or C_2-C_{20} alkynyl.

96. The method of claim 19 wherein said R_4 is a hydroxyl group protected with C_1-C_{10} alkyl, C_2-C_{10} alkenyl or C_2-C_{20} alkynyl;
further comprising the step of deprotecting said R_4 with a deprotecting reagent.

97. The method of claim 96 wherein said deprotecting reagent is an aqueous amine.

98. The method of claim 97 wherein said amine is piperidine, pyrrolidine, piperazine or morpholine.

99. The method of claim 96 wherein said deprotecting reagent comprises an aqueous amine and a mercapto compound.

100. The method of claim 99 wherein the concentration of said mercapto compound is 2-10%.